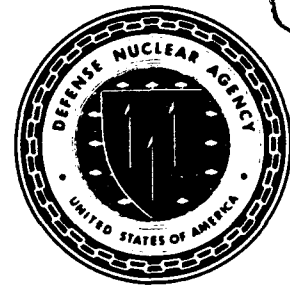


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**DNA-TR-91-47**

## **Effects of Ionizing Radiation on Auditory and Visual Thresholds**

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**March 1992**

**Technical Report**



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REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503				
1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE 920302	3. REPORT TYPE AND DATES COVERED Technical 871009 - 910528		
4. TITLE AND SUBTITLE  Effects of Ionizing Radiation on Auditory and Visual Thresholds		5. FUNDING NUMBERS C - DNA 001-87-C-0277 PE - 62715H PR - RM TA - RF WU - DH191900		
6. AUTHOR(S)  Robert D. Hienz				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Johns Hopkins University School of Medicine 720 Rutland Avenue Baltimore, MD 21205		8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Defense Nuclear Agency 6801 Telegraph Road Alexandria, VA 22310-3398 AFRRI (EA) Collins		10. SPONSORING/MONITORING AGENCY REPORT NUMBER  DNA-TR-91-47		
11. SUPPLEMENTARY NOTES This work was sponsored by the Defense Nuclear Agency under RDT&E RMC Code N4662D RM RF MRCO 1160A 25904D.				
12a. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution is unlimited.			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words) An experimental analysis of the effects of low-dose ionizing radiation on sensory and motor function was conducted in baboons. Animals were trained using a reaction time procedure to respond to near-threshold acoustic and visual stimuli, and quantitative assessments were made of radiation-induced changes in absolute auditory and visual thresholds and reaction times. Animals received multiple exposures at single fractionated dose levels of 1, 2, and 5 Gy. Single exposures at higher exposure levels of 10 and 15 Gy were also examined. 100-200 cGy exposures produced transient changes in reaction times. Transient increases in reaction times occurred following low-dose exposures, usually within 1-3 weeks following the exposure. These increases typically recovered to normal baseline levels within 2-3 weeks. 1000 and 1500 cGy exposures produced long-term hearing deficits which were not frequency-specific. The severe hearing loss was most likely due to a sensorineural deficit, since complete loss of function of the tympanic membrane or middle ear ossicles would be expected to produce a hearing loss about 50-55 dB. These higher radiation doses have had less of an effect on visual intensity thresholds, producing a 5-10 dB deficit in visual thresholds. No physical damage to the cornea, iris, lens, or retina was observed.				
14. SUBJECT TERMS Behavioral Analysis      Sensory-motor Functions Reaction Time      Auditory-visual Thresholds			15. NUMBER OF PAGES 44	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT UNCLASSIFIED	18. SECURITY CLASSIFICATION OF THIS PAGE UNCLASSIFIED	19. SECURITY CLASSIFICATION OF ABSTRACT UNCLASSIFIED	20. LIMITATION OF ABSTRACT SAR	

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## SUMMARY

An experimental analysis of the effects of low-dose ionizing radiation on sensory and motor function was conducted in baboons. Using behavioral procedures, animals were trained using a reaction time procedure to respond to near-threshold acoustic and visual stimuli, and quantitative assessments were made of radiation-induced changes in absolute auditory and visual thresholds. Motor function was also assessed by examining reaction times to the auditory and visual stimuli at constant stimulus intensity levels.

Sensory thresholds were measured using a self-paced reaction time procedure, in which an animal initiated each of a series of discrete reaction time trials by pressing and holding down a lever when a "ready" signal was presented, and releasing the lever only when the "reaction time" stimulus occurred. Correct detections of the test stimulus were defined as lever releases occurring during the 1.5 sec stimulus, and were reinforced with banana-flavored food pellets. Detection thresholds for both pure tones (16 kHz) and white light stimuli were determined by randomly varying stimulus intensity from trial to trial, and examining detection frequencies (i.e., percent correct lever releases) for each intensity. To measure the false alarm or "guessing" rate of each subject, "catch" trials (no-stimulus trials) were interspersed among the normal trials during testing sessions. In addition, reaction times, defined as the elapsed time between signal onset and lever release, were recorded to the nearest millisecond on all trials.

X-ray radiation exposures were carried out in the Radiation Therapy Division of the Oncology Center at Johns Hopkins Hospital. A 4 MeV clinical linear accelerator (Varian CLinAC 4-100) calibrated to national standards on a weekly basis, provided x-ray exposures at a dose rate of 175 cGy/min. Radiation exposures were head-focus only to eliminate generalized effects of whole-body radiation. Technicians followed the same procedures employed with human patients. Doses were calibrated at the midplane of the calvarium. Animals were sedated with ketamine (i.m.) to prevent movement during exposure. One-half of the beam time was from one lateral field, and one-half from the other lateral field. Animals were visually monitored during exposures via a closed-circuit video system. Animals received multiple exposures at single fractionated dose levels of 1, 2, and 5 Gy, with intervals of 1-3 months separating successive exposures. Single exposures at higher exposure levels of 10, 12 and 15 Gy were also examined. Total cumulative doses examined ranged from 20 to 65 Gy, spaced over periods of up to 2 years.

Regarding exposure effects on reaction times, subjects showed the transient improvements in reaction times which start on the day after an exposure, and last for a minimum of 2-3 days and a

maximum of a few weeks. In terms of decremental effects on reaction times, subject PA showed instances of marked temporary elevations in auditory reaction times. These reaction time elevations did not occur immediately following an exposure period, but started 1-3 weeks following the last exposure. For one subject, the last episode of reaction time elevations required 75 days before full recovery was evident. Such long-term changes were not observed with the testing of visual reaction times. Transient visual reaction time elevations were observed for subjects SO and SK, with reaction times markedly elevated on the first day following exposures, but returning to normal levels within the next 2-3 days.

Higher radiation exposures (10, 12 and 15 Gy) produced long-term hearing deficits, with the higher exposure dose producing more severe hearing deficits (>90 dB hearing losses). This hearing loss was not frequency-specific. The severe hearing loss was most likely due a sensorineural deficit, since complete loss of function of the tympanic membrane or middle ear ossicles would be expected to produce a hearing loss about 50-55 dB. Single dose exposures have considerably less of an effect than multiple exposures, although single doses at 12 and 15 Gy still result in sizeable temporary hearing losses, but only modest permanent hearing losses. The higher radiation doses have less of an effect on visual intensity thresholds, producing a 5-10 dB deficit in visual thresholds. No physical damage to the cornea, iris, lens, or retina were observed. The vowel discrimination data indicate no differences in the acquisition of these vowel discriminations following single exposures of up to 15 Gy. Based on estimates of frequency discrimination capabilities from formant shifts in steady-state vowels, it appears that there are no obvious effects of these radiation exposure levels on the frequency resolving power of the monkey auditory system.

## PREFACE

Research was conducted according to the principles enunciated in the "Guide for the Care and Use of Laboratory Animals", prepared by the Institute of Laboratory Animal Resources, National Research Council.

We wish to acknowledge the contributions of A. Budnick, D. Bowers, D. Gurley, and D. Spear for technical assistance; and Drs. B. May, D. Mattox, and L. Cork for their collaborative efforts.

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## SECTION 1

### INTRODUCTION

While extensive research has been carried out on the effects of ionizing radiation on numerous aspects of human health (e.g., increased cancer and genetic risk factors; 1,2), relatively little is known about radiation's specific effects on aspects of sensory or motor functioning. Numerous studies have examined the effects of radiation on neural function (e.g., as reviewed in 3), inferring from these changes the likely behavioral functions affected by radiation in an intact organism. A direct assessment of functional alterations in the intact organism as a result of radiation exposure, however, can be provided by a behavioral analysis of the sensory and motor performances of an organism. Relatively little work, however, has been carried out in this area regarding the effects of ionizing radiation, especially with respect to the more precise animal psychophysical procedures that have been developed over the last two decades. The present report addresses these issues by providing an experimental analysis of the effects of ionizing radiation on sensory and motor function in non-human primates.

There are data (reviewed by Kimmeldorf and Hunt; ref 3) suggesting that alterations in auditory and visual function follow exposure to ionizing radiation. For visual function, such evidence includes 1) the temporary loss of scotopic visual sensitivity in humans 1 day after exposure to approximately .3 and 1 Gy (x-rays); 2) impaired discrimination learning in rats of shades of gray after exposure to 3 Gy; and 3) deficits in visual acuity in monkeys following whole-body exposures of 3 Gy or 6 Gy. For auditory function, such evidence includes 1) extensive damage in the inner ears of rats following doses of 1 Gy to 29 Gy, with the damage being mostly hemorrhage, but including edema and destruction of the organ of Corti; 2) the induction of "radiation otitis media" in human patients after exposure to 38-57 Gy, including loss of sensitivity, earache, tinnitus, and evidence for acoustic hypersensitivity (auditory recruitment); and 3) disturbances in cochlear microphonics suggestive of a 4-9 dB hearing loss in guinea pigs for pure tones in the 500-8000 Hz range. On the other hand, transient "improvements" in auditory sensitivity (i.e., lower thresholds) have been reported in dogs at single doses of .7-6 Gy and in pigeons following head exposures of 5 Gy, although no such improvements were observed with goats following exposures of 1 Gy (whole body).

The development of psychophysical procedures for use with animals over the last two decades has made possible the precise measurement of sensory function in a wide variety of species (4-7). The training and testing procedures employed are well documented (8,9), and several studies have

demonstrated the sensitivity and specificity of such procedures in behavioral pharmacology applications (10-14). Research reported over the past several years from our laboratory at the Johns Hopkins University School of Medicine has focused on the development and application of such a methodology for assessing the effects on sensory and motor function of drugs that are self-administered by animals and abused by man (13-20). This methodology has now been applied to an analysis of the effects of ionizing radiation on sensory and motor function in nonhuman primates.

## SECTION 2

### METHODS

#### 2.1. SENSORY THRESHOLD AND REACTION TIME DETERMINATIONS.

##### 2.1.1. General Procedure.

The psychophysical methodology involved the use of a reaction-time procedure which required baboons to press a lever and hold it depressed for varying intervals until presentation of a light flash or tone burst signaled the availability of food reward following lever release. Correct responses were defined as lever releases occurring within 1.5 sec of stimulus onset and were rewarded with banana-flavored food pellets. Detection thresholds were determined by systematically varying stimulus intensity and recording the frequency of correct and incorrect responses (i.e., lever releases occurring later than 1.5 sec after stimulus onset). In addition, response latencies (i.e., elapsed time between signal onset and lever release) were recorded to the nearest millisecond as a measure of reaction time.

##### 2.1.2. Subjects and Apparatus.

The subjects were dog-faced baboons (*Papio* species), housed in individual cages and maintained on a restricted feeding schedule with supplemental monkey chow and fresh fruit provided on a daily basis after each experimental session. The testing apparatus consisted of a modified baboon squeeze cage fitted within a double-walled sound attenuating chamber (IAC-1201 A). A 76 x 97 cm intelligence panel attached to one side of the cage contained a primate lever (BRS/LVE Model PRL-003), a red light-emitting diode used as a cue light, a 2.5 cm diameter opaque plexiglas visual stimulus patch, and a tube feeder for delivery of banana pellets. With the animal positioned facing the panel, the cue light and visual stimulus patch were at eye level, the feeding tube at mouth level, and the response lever at waist level in front of the right arm. When the animal's mouth was just touching the tube feeder, the visual angle between the cue light and the visual stimulus patch was approximately  $15^{\circ}$ . A wide-range speaker suspended outside the cage and located directly over the animal's head approximately 20 cm above ear level provided for the delivery of auditory signals. Animals were transported into the experimental apparatus for testing via a small transfer cage; during testing the animals were observed via a closed-circuit infrared T.V. monitoring system.

##### 2.1.3 Sensory Stimuli.

The light source for the visual stimuli was a slide projector mounted on the outside of the chamber that projected white light onto the back of the stimulus patch through an otherwise light-tight aperture in the chamber wall. Stimulus intensity was varied by using neutral density filters in the

slide projector. Light intensities were calibrated with a light meter (Model 40x, United Detector Technology). Acoustic signals were generated by a Krohn-Hite oscillator passed through an electronic switch (20 msec rise and fall times), programmable attenuator, amplifier, and finally, through the wide range speaker. The system was calibrated with a General Radio sound level meter, a Bruel and Kjaer amplifier, and 1.25 cm condenser microphone located at ear level facing the speaker. Experimental contingencies and data collection were accomplished by laboratory-based computers.

#### 2.1.4 Procedure.

Details of the reaction time procedure were as follows: In the presence of a flashing red cue light (5/sec), a lever press changed the flashing red light to a continuous red light which remained steady as feedback as long as an animal held the lever down. At intervals ranging from 1.0 to 7.3 sec after initiation of this maintained holding response, a stimulus (white light on the circular patch during visual threshold testing, or tone burst through the speaker during auditory threshold testing) was presented for 1.5 sec. Release of the lever within the 1.5 sec stimulus interval delivered the reinforcer (a 500-mg banana-flavored pellet) and initiated a 3-sec intertrial interval (ITI) during which no stimuli were presented and lever responses re-initiate the ITI. Lever releases prior to stimulus onset produced a 5-sec timeout, then reinstated the 3-sec ITI without reinforcement. If an animal failed to release the lever during a stimulus, the red cue light was turned off following stimulus offset, and lever release then returned the animal to the ITI. Following the end of the ITI, the flashing red cue light signaled initiation of the next trial in the series of several hundred which comprised each daily two-hour experimental session.

#### 2.1.5 Threshold Determinations.

Auditory and visual thresholds were determined by randomly varying the intensity of the test stimuli from trial to trial in accordance with the method of constant stimuli, and examining detection frequencies (i.e., percent correct lever releases) at each intensity. For the auditory modality, four intensity levels (10 dB apart) of a 16.0 kHz pure tone were used, with the lowest level set just below an animal's estimated threshold. Although the use of these step sizes requires interpolation for defining thresholds, they were used for two reasons: 1) Smaller step sizes at near-threshold stimulus levels result in a greater frequency of unreinforced trials, which commonly leads to increased variability of performance and loss of stimulus control. 2) One can obtain a reliable and precise estimate of the 50% detection level typically used to define threshold by obtaining 2 points along the steep portion of the S-shaped psychometric function. Care was taken to insure that the 2 points used to estimate the 50% detection point lay on the steep part of the curve and not near the asymptotic ends of the function. Typically, the lowest intensity was adjusted to

produce a detection level of about 25-35%, with the next higher intensity adjusted to produce a detection level of about 70-80%. For the visual modality four intensity levels (0.5 log density units apart) of white light were used, with the lowest level set just below the animal's estimated threshold. To measure the false alarm or "guessing" rate, interspersed among both the auditory and visual test trials were a series of "catch" trials during which no stimuli were presented. Lever releases during catch trials were punished with a 3-sec timeout.

Auditory and visual thresholds were determined in separate sessions, with each test session divided into blocks of 140 trials with each of the four intensity levels plus "catch" trials presented randomly approximately 28 times during each block. Four to five such blocks of trials occurred within each session to provide a number of independent within-session estimates of the sensory thresholds and functions relating reaction time to intensity. Sensory thresholds were determined from percent correct detections at each intensity by interpolating to the intensity that produced a detection score halfway between the false alarm rate and 100%. Thresholds prior to exposure were considered stable only when a session contained three or more successive threshold estimates that varied by no more than  $\pm 0.125$  log density units for visual thresholds, and by no more than  $\pm 2$  dB for auditory thresholds. In both cases, such a determination of threshold stability required a false alarm rate below 30% for each block of trials within a session, and no systematic changes in either thresholds or reaction times. Since reaction time distributions are typically skewed due to the physiological limits on lever release time, the standard measure of central tendency employed was the median, with variability measured in terms of the interquartile range. Reaction times were considered stable when all successive median reaction times for the highest stimulus intensity were within 50 msec of one another for all test blocks of a session.

Since absolute visual threshold testing requires a completely darkened experimental chamber and a dark-adapted animal, normal testing was started only after a 30 min period of adaptation to the chamber. Additionally, to make the data as comparable as possible between the auditory and visual modalities, auditory threshold testing sessions were conducted in an identical manner (i.e., in a dark chamber with a 30-min adaptation period prior to formal testing). In order not to appreciably affect the time course of dark adaptation, the cue light used to signal trial initiations was a small, dim red light.

#### 2.1.6 Data Analysis.

The basic data employed were percent correct lever releases to the various intensity levels of the auditory and visual stimuli during their respective testing sessions, as well as median reaction times to each stimulus intensity and the variability in reaction time (i.e., the interquartile range as specified by the first and third quartiles of each reaction time distribution). The false alarm rate,

defined as the percentage of no-stimulus trials to which an animal releases the lever, was also measured. Observations of an animal's condition and behavioral performance were taken both during and after each session.

Routine data analysis consisted of examining changes in absolute sensory thresholds, reaction times to correctly-detected stimuli, and false alarm rates as a function of exposure dose and time since exposure. These functions were contrasted with similar data from the pre-exposure control sessions. Both psychometric functions and reaction time functions were examined for possible effects on these measures at different intensities of the sensory stimuli.

## 2.2 SPEECH SOUND DISCRIMINATIONS.

### 2.2.1 Stimuli.

Steady-state vowels were chosen as the speech stimuli for three reasons. First, compared to other speech sounds synthetic steady-state vowels can be more easily matched in terms of their overall durations and intensities, thereby insuring behavioral discriminations based on the spectral characteristics of the stimuli, and not on minor differences in intensities or durations. Second, steady-state vowels are more easily analyzed in terms of their spectral characteristics since their waveforms repeat themselves and typically do not have sharp transients. Third, the degree of difficulty of the discriminations can be adjusted by selecting stimuli with first and second formant frequencies either closer to or farther from a given standard vowel.

### 2.2.2 Procedure.

Vowel discriminations were conducted using the standard reaction time procedure. Throughout the entire session a background train of one vowel sound was presented (e.g., /a/ as in "cat"). This standard vowel was presented at a rate of 2/sec, with a duration of 250 msec. An animal pressed and held down the reaction time lever for a variable period, and released the lever when the background vowel changed from the standard to 1 of 4 randomly chosen comparison vowels (e.g., from /a/ to /e/, as in "let"). The comparison and standard vowel alternated for 2 alternations, following which only the standard vowel occurred. A correct detection of the vowel change was a release of the lever within 1.5 sec of the first occurrence of the comparison vowel. Contingencies for early releases and false alarms were identical to those used in the standard reaction time procedure discussed above. Additionally, reaction times were measured from the onset of the first presentation of the comparison vowel to subsequent lever release. Example words containing the vowel sounds used are: "caught" - background vowel; and "let," "lot," "book," and "cat" - comparison vowels. Changes in the first formants of these comparison vowels from the background vowel are approximately 43, 56, 130, and 133 Hz, respectively. (See Table 3,

for formant specifications of all vowels.)

### 2.3 IONIZING RADIATION EXPOSURES.

X-ray radiation exposures were carried out in the Radiation Therapy Division of the Oncology Center at Johns Hopkins Hospital, under the supervision of Dr. Moody Wharam. A clinical linear accelerator (Varian CLinAC 4-100), calibrated to national standards on a weekly basis, provided x-ray exposures at a dose rate of 2 Gy/min. Radiation exposures were head-focus only to eliminate generalized effects of whole-body radiation. Technicians followed the same procedures employed with human patients. Animals were sedated with ketamine (i.m.) to prevent movement during exposure. One-half of the beam time was from one lateral field, and one-half from the other lateral field. Doses were calibrated at the midplane of the calvarium. Portal films and treatment calculations were recorded for all exposures. Animals were visually monitored during exposures via a closed-circuit video system.

The general procedure for evaluation of ionizing radiation effects was based on a within-subject design in which a single, fractionated exposure was given (e.g., 100 cGy), followed by extensive daily testing of sensory and motor function for a variable period of time (e.g., weeks to months), followed by a repeat exposure at the same fraction. In all cases, the determining factor in the time intervals between successive exposures was the stability of each animal's performance baseline. For example, if a given dose had no effect on either sensory or motor function for the 2-3 week period following exposure, then the exposure dose would be repeated. If, on the other hand, sensory or motor function changes were evident, these changes were examined over time until an animal's performance returned to normal, or (in the case of permanent changes) the performance measures stabilized at a constant, new level. When a single, fractionated dose appeared to have no effect on sensory/motor function after repeated exposures, the dosing fraction was increased (e.g., from 100 cGy to 200 cGy), and the experimental protocol repeated. In this manner, animals received multiple exposures at single fractionated dose levels of 100, 200, and 500 cGy over the contract period, with intervals of 1-3 months separating successive exposures. Single exposures at higher exposure levels of 10, 12, and 15 Gy were also examined. Total cumulative doses examined ranged from 20 to 65 Gy, spaced over periods of up to 2 years. A detailed statement of exact exposure histories and total cumulative doses given are shown in Tables 1 and 2.

**Table 1. Exposure histories.**

ANIMAL	# OF EXPOSURES AT FRACTIONATED DOSES:					
	1 GY	2 GY	5 GY	10 GY	12 GY	15 GY
PA	8	6	4	1	-	1
SK	6	2	4	1	-	1
SO	-	2 (@2.5 Gy)	1	1	-	-
JE	-	-	-	-	1	-
EE	-	-	-	-	-	1

**Table 2. Total cumulative doses.**

ANIMAL	DOSE
PA	65 GY
SK	55 GY
SO	20 GY
JE	12 GY (Single Dose)
EE	15 GY (Single Dose)

Prior to actual radiation exposures, non-exposure control sessions were conducted in a manner identical to actual radiation exposures for each animal (i.e., animals were sedated, transported to the radiation facility, and restrained, without receiving an actual exposure), and the effects of these control manipulations was also evaluated with the psychophysical testing procedures.

Experimental radiation exposures occurred only after normal, stable thresholds and reaction times were obtained during baseline control sessions. Sessions were conducted daily, and normally ended after the completion of four successive test blocks, or two hours, whichever occurred first.

## SECTION 3

### RESULTS

#### 3.1 BASIC MEASURES.

Figure 1 shows the basic types of data collected with the present psychophysical procedures. The psychometric function (left) is a plot of percent correct detections as a function of stimulus intensity, which decreases with decreasing stimulus intensity. The false alarm rate is the percent

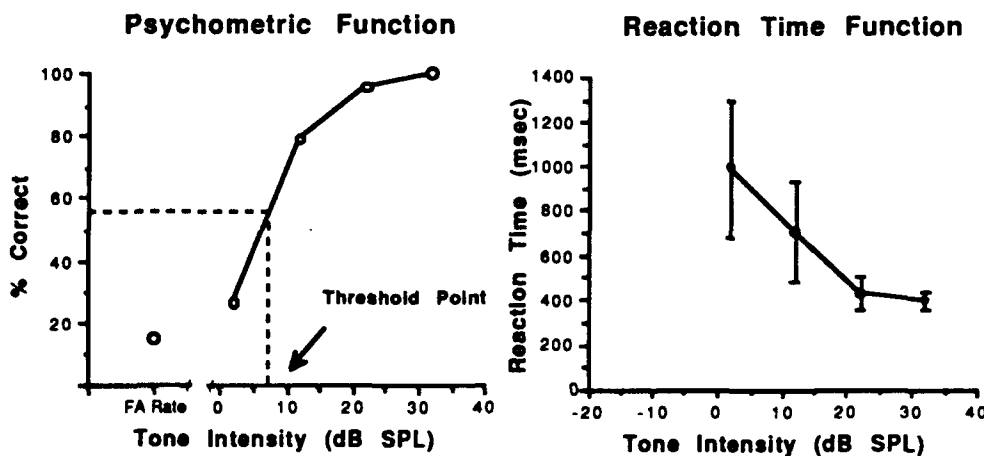


Figure 1. Left Panel: Psychometric function for a baboon on an auditory detection task. Percent correct detections are plotted as a function of stimulus intensity; the unconnected point labelled FA rate indicates the false alarm (or guessing) rate when no stimuli were presented. Right Panel: Reaction time function for a baboon on an auditory detection task. Median reaction times are plotted as a function of stimulus intensity. Error bars encompass the interquartile range (middle 50% of the reaction time distribution) at each intensity. Ranges indicate that variability is usually least with more intense (louder) stimuli.

lever releases on trials where no tones were presented, and indicates the degree to which an animal may "guess" on any particular trial. The threshold point is defined as the intensity producing a detection score halfway between the false alarm rate and 100%; this definition normalizes the psychometric function for different false alarm rates which might occur among different animals or across different conditions, etc. The reaction-time function (right) is a plot of median reaction times (RTs) as a function of stimulus intensity, with error bars indicating the interquartile range (middle 50% of the frequency distribution). RTs are for correctly detected stimuli only; consequently, as stimulus intensity and percent correct scores decrease, the number of RTs contributing to the median estimate also decreases. Both median RT and the interquartile range

normally decrease with increasing stimulus intensity. Typically, the highest of the 4 stimulus intensities presented (right-most point in the graph) is used as an indicator of motor performance, since variability is minimal at this intensity. The median RT at this highest stimulus intensity is then averaged for successive blocks of trials within each session to produce an overall mean RT for the session.

### 3.2 CONTROL PROCEDURES.

First experimental tests with each experimental subject involved "dry run" control sessions during which baboons were anesthetized with the appropriate doses of ketamine and atropine, with diazepam (valium) used when needed to prolong the anesthetic effects and act as a muscle relaxant. Baboons were then transported to the radiation exposure facility, placed on the exposure platform, had portal films taken to insure proper head placement, but received no actual experimental radiation exposures. These control sessions revealed an initial "day-after" effect of a shortening of reaction times, presumably due to the ketamine anesthetic used during these control session non-exposure tests. These effects were transient, however, with reaction times returning to normal levels by the second day post-test. No changes in auditory thresholds or in the animals' general performances were observed during these control studies.

### 3.3 MOTOR FUNCTION EFFECTS.

**3.3.1 Short-term Motor Function Improvements.** The first series of actual radiation exposures consisted of exposure levels of 1 Gy per exposure for two baboons (PA and SK). For baboon PA, no performance changes were observed following the first radiation exposure. Following the second exposure one week later, however, a pronounced decrease in auditory reaction times occurred that continued for 6 days post-exposure. Figure 2 shows these changes, plotting mean reaction time at the highest stimulus intensity for each of a series of consecutive sessions. Open symbols indicate a series of sessions preceded by the administration of ketamine only; filled symbols indicate those series of sessions preceded by the administration of ketamine plus exposure to the indicated radiation dose. [Graphs included in this report show changes in reaction times and/or auditory and visual thresholds across sessions. In some instances, breaks in the curves represent not only occurrences of radiation exposures, but also other manipulations such as control exposures, physical health checks, equipment malfunctions and/or changes, etc. In all cases, consecutive points represent data from consecutive sessions, although there may have been intervening days when no sessions occurred (as during actual radiation exposure days, periodic TB testing, equipment malfunctions, etc.).

Throughout this series of exposures, auditory thresholds and other performance measures remained normal. Similar results were observed following the third and fourth exposures (i.e., shortened reaction times that did not return to baseline levels for a number of days). Body weight checks during this time did not reveal any weight losses that might have contributed to this unusual effect.

Since the ketamine anesthetic employed to sedate animals during radiation exposures occasionally produced a transient, 1-day decrease in reaction times during control sessions, additional baseline control tests were conducted to determine whether or not these long-lasting reaction time decreases following radiation exposures were due to 1) a combination of the radiation exposures and the

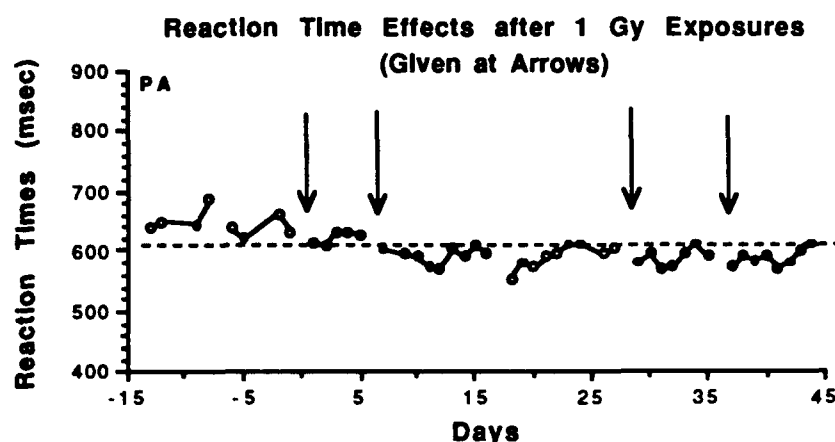


Figure 2. Mean auditory reaction times across individual sessions for baboon PA following 1 Gy exposures (indicated by arrows). Breaks in the function indicate anesthesia administration. Open symbols show reaction times following ketamine administration; closed symbols show reaction times following ketamine administration plus radiation exposure.

anesthetic, or simply due to 2) some type of "sensitization" effect of repeated use of the anesthetic. Results indicated that baboon PA appeared sensitive to anesthetic doses given often, and that when such doses were more spaced in time (e.g., 2 weeks or more) the long-lasting decreases in reaction times following ketamine alone were not observed. The continued presence of these long-lasting decreases in reaction times, however, suggests that this effect may be due to an interaction of the anesthetic plus the exposure. On the other hand, data from baboon SK during initial non-exposure control sessions showed no initial day-after effects of the ketamine anesthetic. However, this subject also showed small reaction time decreases starting on the second day after both the first and second exposures at 1 Gy that returned to baseline levels within 1-2 days. Figure 3 shows these changes, plotting mean reaction time at the highest stimulus intensity for each of a series of

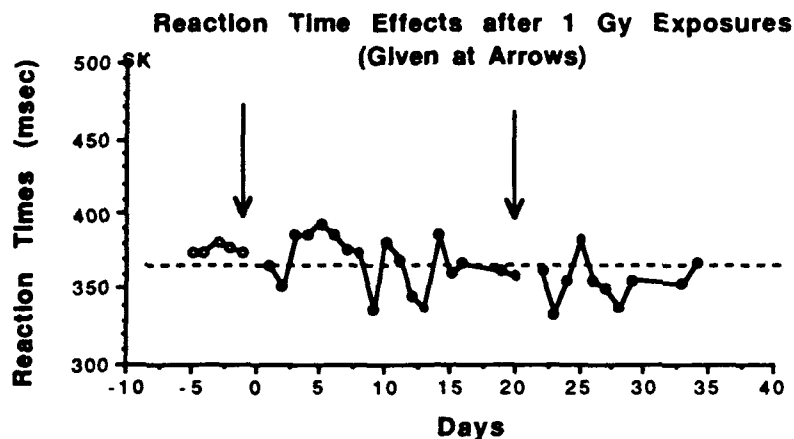


Figure 3. Mean auditory reaction times across individual sessions for baboon SK following 1 Gy exposures (indicated by arrows). Further description as in Figure 2.

consecutive sessions. Throughout these exposures, auditory thresholds and other performance measures remained normal.

### 3.3.2 Short-term Deficits in Reaction Times.

Due to the lack of major significant decrements in either sensory or motor function following repeated exposures at the 1 Gy level, exposure levels for baboons were subsequently increased to 2 Gy/exposure. For baboon PA, the fifth exposure at 2 Gy resulted in a marked increase in auditory reaction times. Figure 4 shows reaction times across 4 series of consecutive sessions for this baboon, including the fifth exposure at 2 Gy (indicated by the second arrow in the figure). Following this dose (a total cumulative dose of 18 Gy), reaction times rose gradually over a period of five days, and were more than 100 msec longer than normal at this time. The maximum

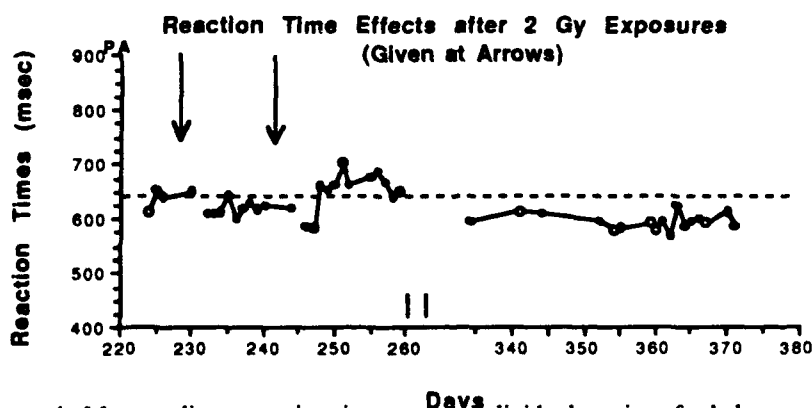


Figure 4. Mean auditory reaction times across individual sessions for baboon PA following 2 Gy exposures (indicated by arrows). Further description as in Figure 2.

observed reaction time change corresponded to about a 20% lengthening in reaction times. Auditory thresholds remained unchanged throughout these sessions.

Another example of such reaction time decrements is shown in Figure 5 for baboon SK. Approximately 4 weeks after this animal's second exposure at 5 Gy, an abnormal increase in reaction times also occurred, with reaction times rising markedly to over 200 msec above baseline conditions (reaction times lengthened by over 60%). A recovery to baseline reaction time levels occurred subsequently. Following this reaction-time recovery period, subject SK received two additional exposures at 5 Gy (for a total cumulative dose of 25 Gy). Following these other exposures, no major long-term changes were seen in reaction times (reaction times remained near baseline levels).

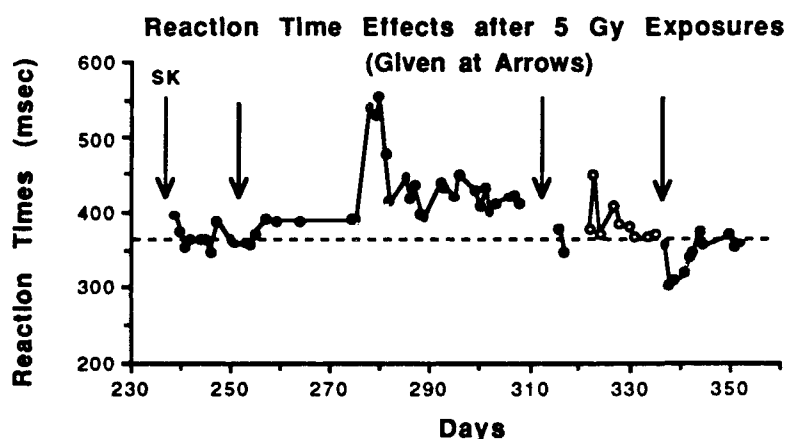


Figure 5. Mean auditory reaction times across individual sessions for baboon SK following 5 Gy exposures (indicated by arrows). Further description as in Figure 2.

### 3.3 Anomalous Single Exposure Effects

Recent analyses of the motor performance effects of baboon JE following a 12 Gy single exposure have revealed some surprising effects. Elevations in reaction times were observed coincident with elevated low-frequency auditory thresholds following radiation (discussed below). Differences have been found, however, for reaction times to clearly audible tones (about 25 dB above normal hearing levels), and reaction times to just audible tones (about 5 dB above normal hearing levels). As can be seen in Figure 6, reaction-time elevations for clearly audible tones peaked within 30-35 days and then gradually recovered to normal over the next 30-35 days. Interestingly, reaction times for those just-audible low-frequency tones showed no such sharp elevation. And

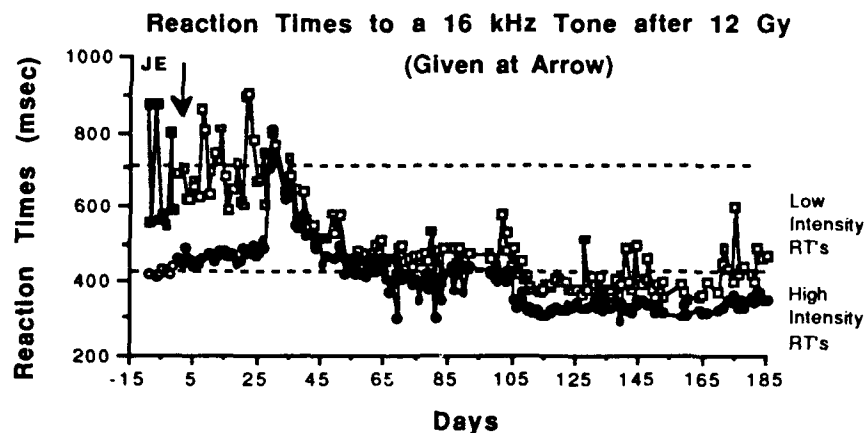


Figure 6. Mean auditory reaction times to a 16 kHz tone across individual sessions for baboon JE. Open circles indicate reaction times for the highest intensity stimulus prior to 12 Gy exposure; closed circles indicate reaction times for the same stimulus after exposure; closed squares indicate reaction times for a stimulus intensity closer to threshold prior to exposure; open squares indicate reaction times for the same stimulus after exposure.

surprisingly, reaction times to just audible high-frequency tones showed eventual signs of improvement when these reaction times approached the reaction time speed normally observed only for the clearly audible tones. This latter effect suggests the possibility of some type of "loudness

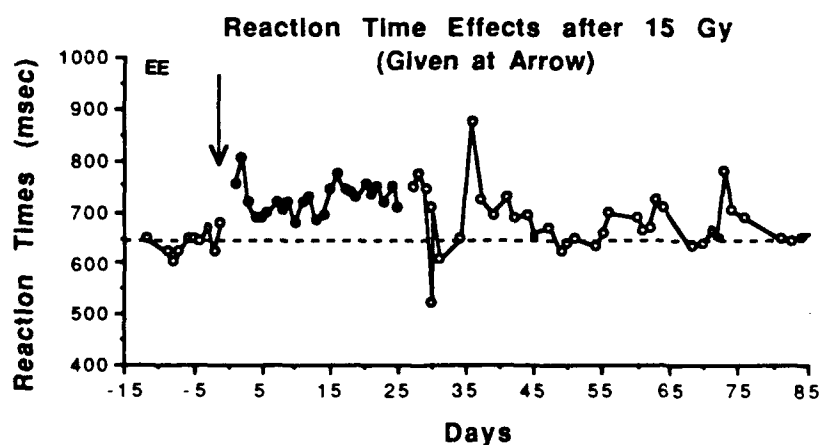


Figure 7. Mean auditory reaction times across individual sessions for baboon EE for a 16 K tone. Open circles indicate reaction times for the highest intensity stimulus prior to 15 Gy exposure; closed circles indicate reaction times for the same stimulus immediately after exposure.

recruitment" occurring during the post-exposure recovery period. This effect was observed at 16 kHz only, where no significant threshold effects were observed.

Similar changes were observed for baboon EE in terms of motor performance deficits (see Figure 7). Following the 15-Gy radiation exposure, this subject showed immediate increases in his reaction time performances that continued to worsen slowly over time. This immediate increase in reaction times was not observed in baboon JE following his single exposure at 12 Gy; the gradual rise in reaction times following exposure was, however, observed in baboon JE. These data indicate that significant differences do exist between the exposure levels of 12 and 15 Gy.

### 3.4 SENSORY FUNCTION EFFECTS.

#### 3.4.1 Auditory Thresholds.

3.4.1.1 Temporary hearing deficits. No hearing deficits were observed at any of the 1 and

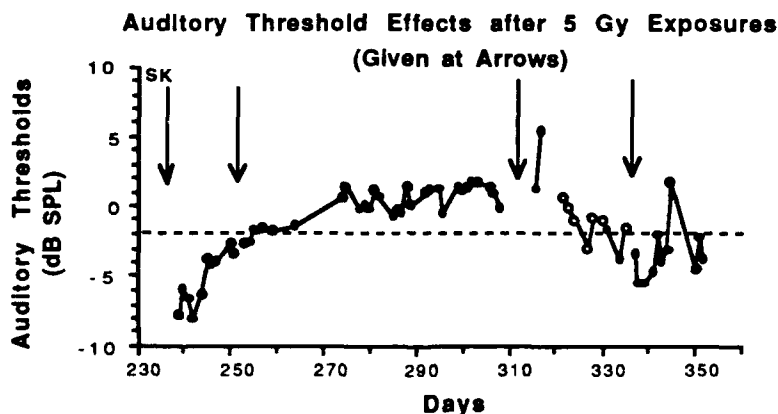


Figure 8. Mean auditory thresholds across individual sessions for baboon SK following 5 Gy exposures. Further description as in Figure 2.

2 Gy exposure levels. The first indication of any change in sensory function was observed in baboon SK after he received his second exposure at 5 Gy (which was after a total cumulative dose of 20 Gy). As shown in Figure 8, after his first 5-Gy exposure, baboon SK showed a slight lowering of auditory thresholds for 4-5 days followed by a gradual return to normal threshold levels. After the second 5-Gy exposure, auditory thresholds remained normal for about 10 days, following which thresholds rose to about 5 dB above normal levels. Auditory thresholds remained at this elevated level for over 2 months. Auditory thresholds eventually recovered, however, so that no permanent changes in auditory thresholds were observed at these exposure levels.

3.4.1.2 Permanent hearing deficits. First evidence for a sustained auditory impairment emerged in subject SK following his fourth exposure at 5 Gy. These data from subject SK are shown in Figure 9, and indicate a hearing deficit of about 8 dB, which began 85 days after the last

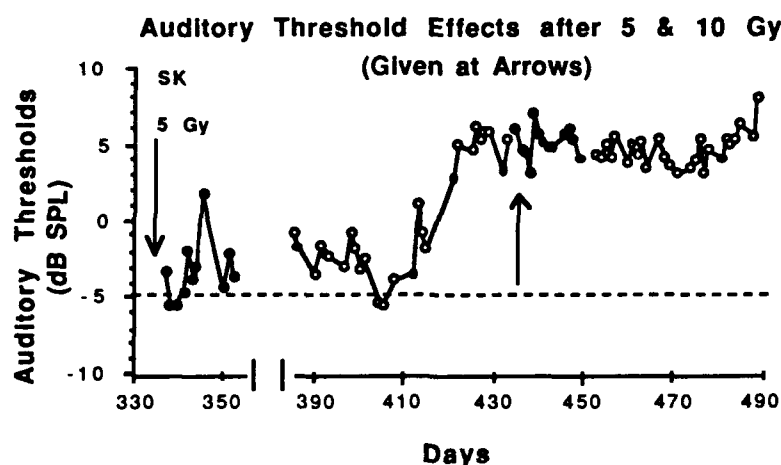


Figure 9. Mean auditory thresholds across individual sessions for baboon SK following 5 and 10 Gy exposures. Further description as in Figure 2.

5-Gy exposure, and persisted thereafter. This permanent hearing loss was recorded after a total cumulative exposure dose of 30 Gy. An additional 10-Gy exposure did not have any further impact on this subject's hearing thresholds (i.e., his hearing did not worsen or improve).

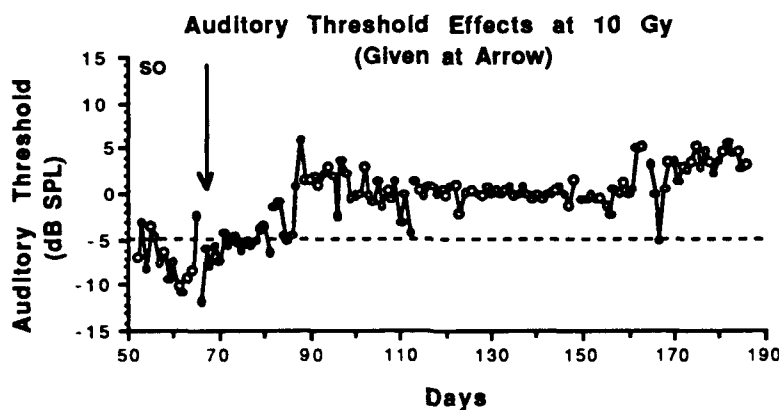


Figure 10. Mean auditory thresholds across individual sessions for baboon SO following 10 Gy exposure. Further description as in Figure 2.

Evidence for a permanent hearing loss at a slightly higher single-exposure dose (but a lower cumulative-exposure dose) can be seen in Figure 10, which shows auditory thresholds across selected consecutive sessions following baboon SO's single exposure at 10 Gy. This baboon had previously received 2 exposures at 2.5 Gy and 1 exposure at 5 Gy; thus a total cumulative dose of 20 Gy had been received by this animal at this time. These data indicate a permanent hearing loss

of 5-10 dB following the 10-Gy exposure which did not evidence itself until approximately 3 weeks following the actual exposure. This small but consistent hearing loss persisted for approximately 1 year, until the animal was sacrificed due to health problems (discussed below).

Due to the modest nature of the changes observed following exposure levels of 10 Gy, further exposures were conducted with an exposure level of 15 Gy. Following a single exposure at 15 Gy in baboon SK, a most dramatic and severe hearing deficit was observed. This large hearing loss is depicted in Figure 11. Nine days following the exposure, auditory thresholds at 16.0 kHz rose dramatically to over 50 dB above normal levels. This severe hearing impairment was also apparent in the animal's home cage behavior, where he showed little or no reaction to sounds from other animals or human technicians unless the sounds were extremely intense. Physical examination of the subject revealed pronounced edema around the eyes, the pinnae, and external

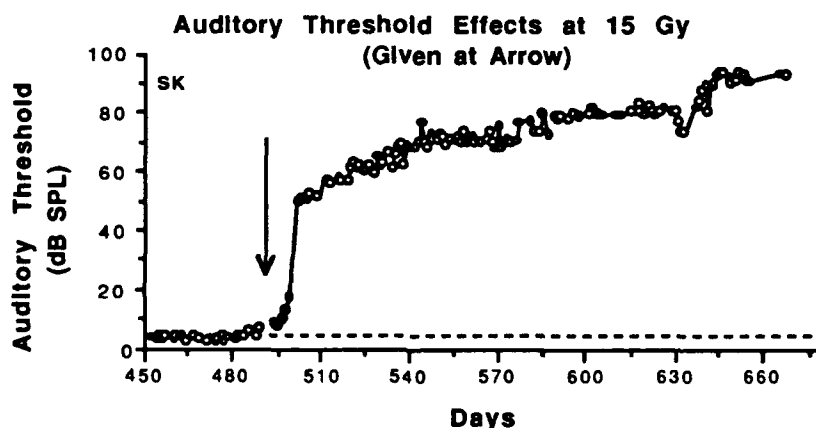


Figure 11. Mean auditory thresholds across individual sessions for baboon SK following 15 Gy exposure. Further description as in Figure 2.

ear canals. This marked edema in the facial area was observed on the first day following exposure, and persisted for approximately 3 months. Signs of lessening of edema in the ear canals was not accompanied by any lessening in the severity of hearing loss. Auditory thresholds continued to rise gradually over a 6-month period, peaking at approximately 90 dB above his normal threshold levels at 16.0 kHz. A human patient with this severe of a loss would be considered clinically deaf. Throughout this period, however, no major changes in reaction times occurred.

Initial observations of the psychophysical performances of baboon PA following his single exposure at 15 Gy paralleled those of subject SK. As shown in Figure 12, auditory thresholds were elevated by 10 dB within 5 days after the exposure, and eventually peaked at about 80 dB above normal levels. Hearing loss in this baboon was quite variable, however, with thresholds fluctuating over time and finally stabilizing at approximately 50 dB above his normal hearing

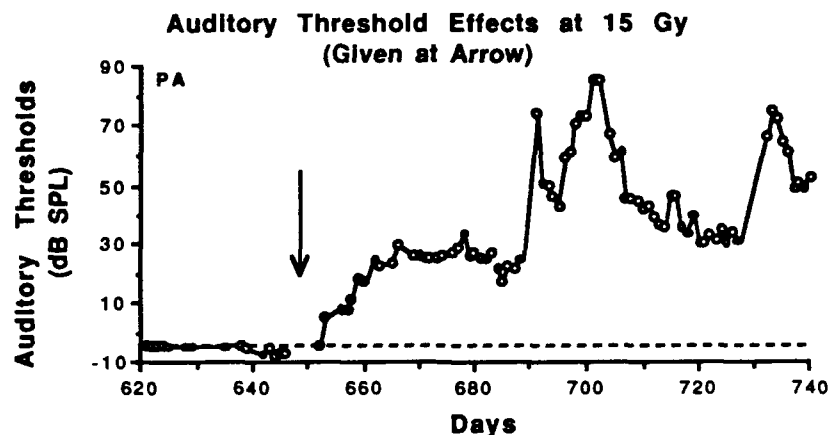


Figure 12. Mean auditory thresholds across individual sessions for baboon PA following 15 Gy exposure. Further description as in Figure 2.

thresholds at 16.0 kHz. Throughout this period of severe hearing loss, auditory reaction times remained relatively unchanged. Baboon PA also showed immediate and severe facial edema, similar to that of baboon SK, which also persisted for approximately 3 months.

Otologic examinations of baboons SK and PA during this period of severe hearing loss revealed severely swollen external ear canals and pinnae. The severity of the loss in subject SK (90 dB), however, was too great to be accounted for by blockage of the ear canals alone. Complete blockage of the ear canals results in sound being transmitted via bone conduction. As bone conduction thresholds are typically about 50-60 dB above normal thresholds, the 90 dB loss in baboon SK exceeds that predicted solely by a completely impacted ear canal. An ear canal block could have, however, accounted for subject PA's hearing loss. Consequently, the aid of a veterinarian and an otolaryngologist was obtained to examine and remove sloughed tissue that had impacted in this animal's external canals. Following this procedure, baboon PA's external ear canals remained clear, as determined by visual inspection, although the severity of the hearing loss continued. The fluctuations in this animal's thresholds were often associated with the administration of the ketamine anesthetic used to sedate the animal for physical examinations. Hearing losses appeared to be more severe for several days after such procedures. No such effects were observed with ketamine prior to this, either in this animal or other animals. Additionally, baboon SK showed no such fluctuating thresholds.

During their last 2 months of testing, the health of baboons PA and SK deteriorated significantly. Approximately 5 months after his 15-Gy head-only exposure, subject PA became extremely ataxic and stopped eating. After extensive examinations and tests by our veterinarians, the decision was made to euthanize the animal. Subject PA's last recorded hearing thresholds indicated a 40-50 dB

hearing loss. During this same period baboon SK suffered a severe stroke, which occurred approximately 6 months after his 15-Gy exposure. This animal suffered complete paralysis of his lower limbs, and partial paralysis in the upper limbs. Initial autopsy reports revealed a lesion in the midbrain near the midline, and a second lesion in the left parietal lobe. Subject SK's last recorded hearing thresholds showed a severe, 90+ dB hearing loss at 16.0 kHz. The health of subject SO deteriorated significantly approximately 1 year following his single exposure to 10 Gy. This subject had extensive health problems over this time period, and therefore did not receive additional exposures. After consultation with veterinarians who followed this subject's health over this 1-year period, the decision was made to euthanize the animal. Subject SO's last recorded hearing thresholds indicated a 10-15 dB hearing loss, which was approximately the same across this animal's hearing range from 250 Hz to 20 kHz. The temporal bones containing the cochleae of all three animals were harvested for later histological examination.

### 3.4.2 Deficits as a Function of Frequency.

Following initial indications of permanent hearing losses, a number of tests were conducted to document more closely the nature and extent of these deficits. First, the psychophysical testing procedures were modified to include a wide range of pure-tone frequencies; in this manner it was assessed whether the hearing losses were a general effect on hearing, or whether the losses were restricted to a particular frequency range (e.g., due to restricted damage to certain portions of the

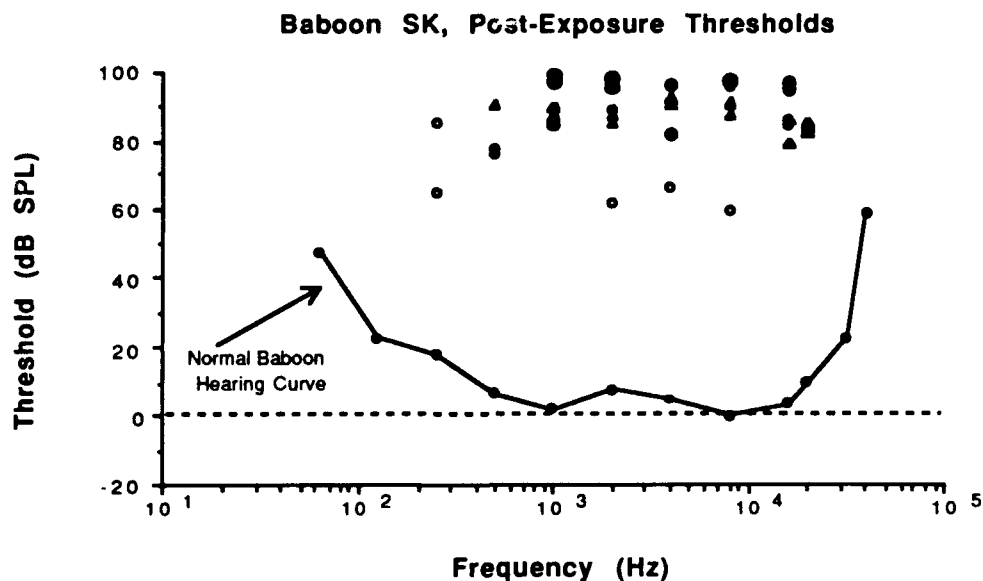


Figure 13. Auditory threshold decrements following radiation exposure as a function of pure-tone frequency within the baboon hearing range for baboon SK. Connected points indicate standard thresholds for normal baboons; unconnected points indicate thresholds for baboon SK after exposures.

cochlea). Test frequencies were expanded to include the octave steps from 250 Hz to 16 kHz, plus 20 kHz. This range encompasses the major portion of the baboon's audibility curve. With this new testing procedure, baboon SK's severe, 90+ dB hearing loss at 16 kHz was found to occur across this range of frequencies, with similar, equally severe hearing losses occurring at all frequencies tested. This wide range of hearing loss is shown in Figure 13, where hearing thresholds are plotted as a function of pure-tone frequency. The solid curve represents the normal baboon hearing curve, while the discrete points represent thresholds obtained 2-5 months following his exposure to 15 Gy. The scatter in the post-exposure threshold points derives from the gradually increasing thresholds that occurred over the extensive time of post-exposure testing

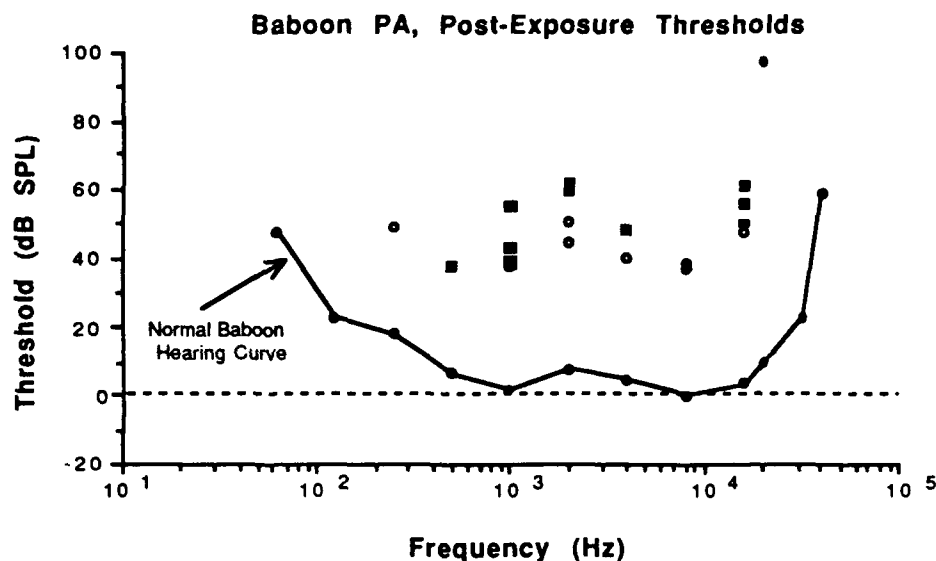


Figure 14. Auditory threshold decrements following radiation exposure as a function of pure-tone frequency within the baboon hearing range for baboon PA. Connected points indicate standard thresholds for normal baboons; unconnected points indicate thresholds for baboon PA after exposures.

(as previously depicted in Figure 11). From Figure 14, one can see that baboon PA's 40-50 dB hearing loss also extended across this animal's hearing range from 250 Hz to 20 kHz. Similarly, hearing losses for subject SO (who showed a smaller 10-dB loss at 16 kHz following a 10-Gy exposure) extended across the range of frequencies tested, as shown in Figure 15.

The severity of the hearing deficit for baboon SK is an indication of the involvement of sensorineural damage in the auditory system. Further, the occurrence of losses across a wide range of frequencies suggests widespread involvement of the cochlea. The severity of the loss in subject SK was too great to be accounted for by blockage of the ear canals alone, as hearing via bone conduction typically occurs at thresholds of 50-60 dB above normal. As a further test of this

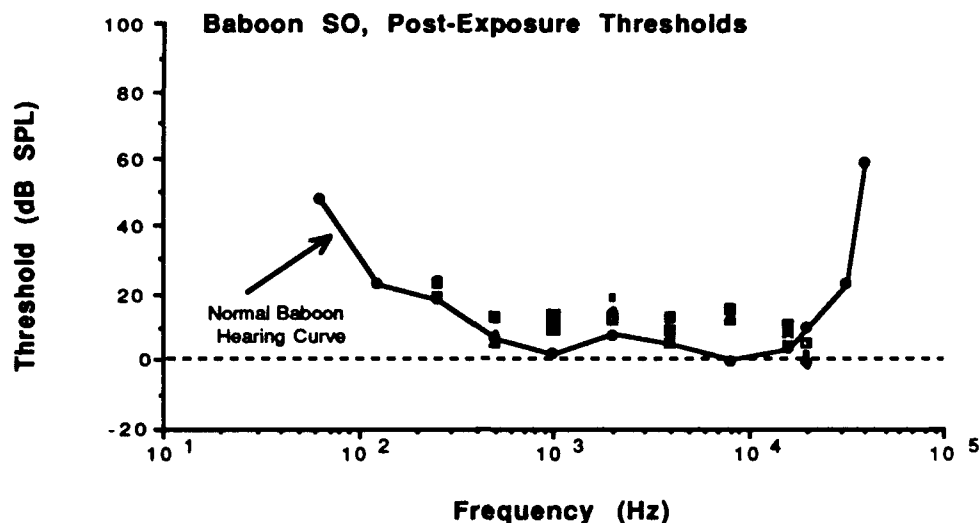


Figure 15. Auditory threshold decrements following radiation exposure as a function of pure-tone frequency within the baboon hearing range for baboon SO. Connected points indicate standard thresholds for normal baboons; unconnected points indicate thresholds for baboon SO after exposures.

possibility, the sloughed tissue that had impacted in this animal's external canals was removed by an otolaryngologist. This animal's severe hearing loss, however, continued.

The magnitudes of the hearing deficits for subjects PA and SO, on the other hand, were well within the limits for deficits produced by dysfunction in the external or middle ear. It is known, however, that low frequencies can readily penetrate blocked ear canals; thus low-frequency thresholds (e.g., at 250 and 500 Hz) should not be much affected by a plugged external ear canal. Both of these subjects, however, showed losses at 250 and 500 Hz that were comparable to the losses measured at other frequencies. These observations suggest that the debris in the ear canals was not the likely sole cause of the hearing losses in these baboons.

The severity of the hearing deficit for these subjects indicated the involvement of sensorineural damage in the auditory system. And the occurrence of losses across a wide range of frequencies suggests widespread involvement of the cochlea. For these reasons the temporal bones containing the cochleae of these animals have been preserved for possible later histological examinations. Additionally, the central nervous system tissues and eyes of these subjects were retained for later examination for possible pathological changes. Results from the initial histological examinations of the brain tissue of subject PA included clear signs of pathological changes in the CNS tissue of this subject, extreme tissue distortion, loss of normal cortical layering patterns in numerous areas, and widespread vascular changes suggestive of a breakdown in the blood/brain barrier. The changes observed have thus far been in agreement with those reported in the scientific literature for the effects of single-dose exposures in primates.

### 3.4.3 Single Exposure Effects.

In an effort to more closely define a single-exposure threshold dose for producing these types of hearing losses, additional subjects were given single dose exposures, head focus only. For these exposures the eyes were blocked in an effort to prevent the chronic inflammation problems experienced in the past with lachrymal ducts. The exposure level was also adjusted in an attempt to more closely define a threshold dose for producing hearing loss. Baboon JE received a single dose of 12 Gy. This subject also received within-session tests of hearing thresholds with both low- and high-frequency tones so that possible differential hearing effects could be tracked throughout the post-exposure period.

Because of this slightly lower exposure dose and the lack of any previous exposures in this subject, it was expected that a longer time course would ensue prior to detecting any significant hearing losses. This indeed was the case. Following the 12 Gy exposure, baboon JE showed no definite signs of hearing loss until 31 days post-exposure, when low-frequency (250 Hz) thresholds began to rise. This rise in thresholds for the 250-Hz tone is shown in Figure 16. This low-frequency hearing loss peaked within the next 4-5 days at a level of approximately 12-13 dB above normal. At the same time, however, high-frequency testing at 16 kHz showed only slight variations in threshold of about 2 dB. Partial recovery of the hearing loss at 250 Hz was seen within the following 20-25 sessions. No further recovery of the hearing loss was observed after this time. Thus a single exposure to 12 Gy appears to be a sufficient dose to produce small, yet permanent hearing loss. Further, the selective change in hearing thresholds at different frequencies

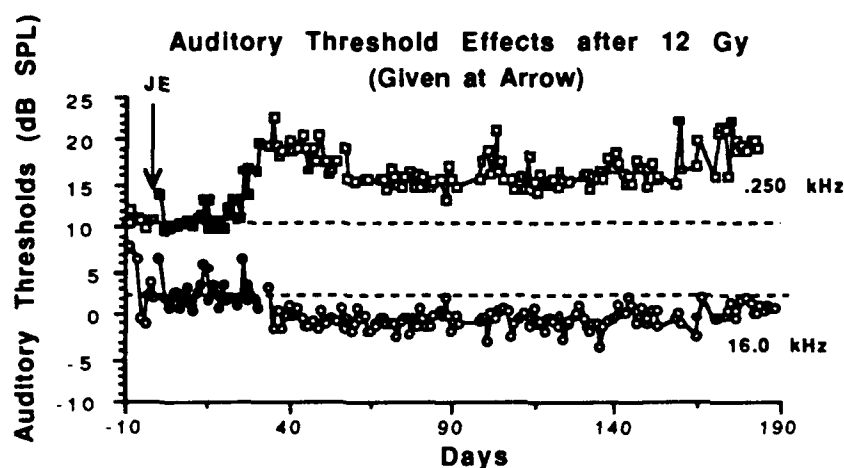


Figure 16. Mean auditory thresholds across individual sessions for baboon JE following a 12 Gy exposure. Upper function indicates thresholds for a 250 Hz tone, bottom function shows thresholds for a 16 kHz tone.

is an indication of a possible differential effect of ionizing radiation on the primate cochlea, since low-frequency hearing takes place near the apical end of the cochlea, and high-frequency hearing occurs at the basal end of the cochlea.

As baboon JE did not show the major hearing losses observed in other subjects, an additional subject, baboon EE, was given a single exposure dose of 15 Gy, head focus only. This subject also received within-session tests of hearing thresholds with both low- and high-frequency tones so that possible differential hearing effects could be tracked throughout the post-exposure period. This baboon began to show initial signs of hearing loss at approximately 20 days, post-exposure, as shown in Figure 17. This compares to a 31-day latency to the first signs of hearing loss following a single exposure to 12 Gy, as reported for baboon JE. A maximum hearing loss of

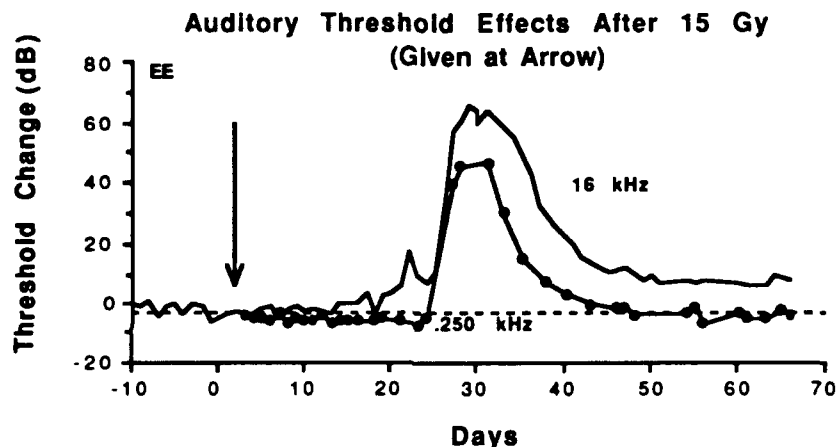


Figure 17. Mean auditory threshold across individual sessions for baboon EE following 15 Gy exposure. Upper function indicates thresholds with a 250 Hz tone, bottom function shows thresholds with a 16 kHz tone.

over 60 dB occurred at 16 kHz. A considerable amount of recovery of this loss occurred subsequently, although a residual hearing loss of about 10 dB remained. Hearing loss also occurred at 250 Hz; at this low frequency, however, there was near-complete recovery over time. The level of hearing loss at 16 kHz exceeded the hearing loss found in baboon JE who received a 12 Gy exposure. Thus there are definite indications of graded increases in the parameters of hearing loss associated with moderate increases in radiation exposure level: that is, hearing losses developed more rapidly, and were more pronounced with this higher exposure level.

### 3.4.4 Visual Thresholds.

3.4.4.1 Deficits at high doses over time. In contrast to the effects of radiation exposures on hearing function, the effects of low-dose exposures of ionizing radiation on visual function were more modest. Temporary changes in visual thresholds were not observed in any baboon. Permanent changes were observed, however, at the higher exposure levels. Following an exposure at 15 Gy, for example, visual threshold sensitivity in baboon SK was reduced, though not as severely as auditory threshold sensitivity. These elevations in visual thresholds are shown in Figure 18. This exposure level produced severe edema around the eyes, which was accompanied by excessive tearing, most likely due to blocked lacrimal ducts. Detailed examination of the eyes by an ophthalmologist revealed no signs of retinal damage, cataract formation, or any

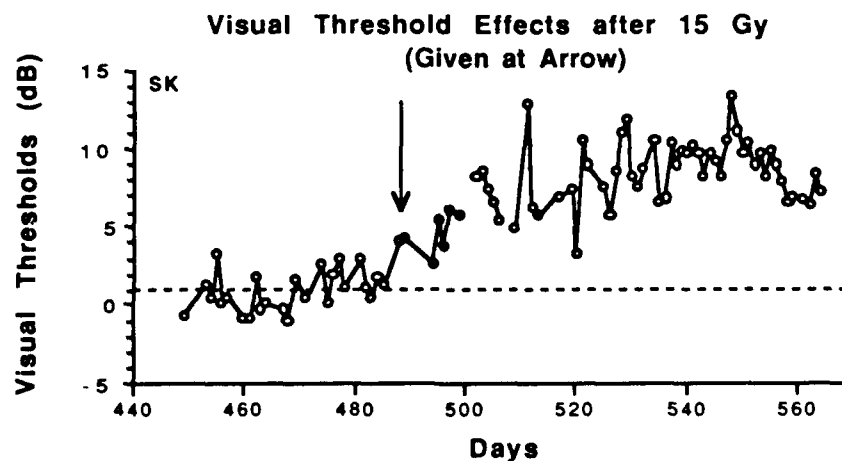


Figure 18. Mean visual thresholds across individual sessions for baboon SK following a 15 Gy exposure (indicated by arrow). Further description as in Figure 2.

other readily observable condition that might account for the visual threshold changes. Partial recovery of the visual threshold changes occurred in the following weeks (while auditory threshold testing continued to indicate a near-deaf subject).

A second example of this type of permanent visual threshold deficit is shown in Figure 19, where following an exposure at 10 Gy, visual threshold sensitivity was compromised in baboon SO. This exposure level also produced moderate edema around the eyes, and was accompanied by excessive tearing. Detailed examination of this baboon's eyes by an ophthalmologist also revealed no signs of retinal damage, cataract formation, or any other readily observable condition that might account for the visual threshold changes. As with the previous subject, partial recovery of the visual threshold changes occurred in baboon SO in the following weeks.

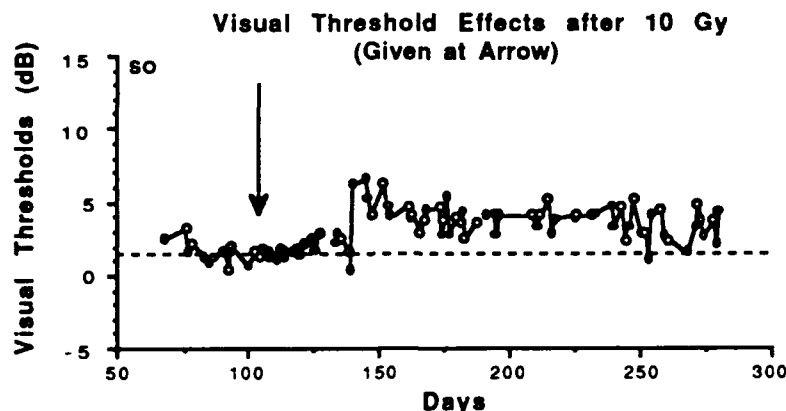


Figure 19. Mean visual thresholds across individual sessions for baboon SO following a 10 Gy exposure (indicated by arrow). Further description as in Figure 2.

### 3.4.5 Complex Auditory Frequency Discriminations.

**3.4.5.1 Speech sound discrimination performances.** It is known that the frequency resolving power of the auditory system diminishes at extremely low, near-threshold sound levels, and also at high sound levels. Thus if an animal is suffering from a severe hearing loss, the perception of speech sounds at normal intensity levels will be compromised due to the loss in hearing sensitivity, and not necessarily to any loss in the frequency resolving power of the auditory system itself. For this reason it was not possible to test the frequency discrimination abilities of those animals experiencing severe hearing losses. Presenting speech stimuli at extremely high sound levels does not get around this type of problem, since normal frequency discrimination abilities fall off at high intensity levels as well. Further, the catastrophic health effects produced by the higher-level radiation exposures made it impossible to continue testing those baboons with significant hearing losses. Evaluations of the frequency resolving abilities were possible for those baboons receiving single exposures that did not compromise their health.

Figure 20 shows the acquisition of vowel discriminations for baboons JE and EE following their single exposures to 12 Gy and 15 Gy, respectively. In this set of vowel discriminations, the standard vowel was au/. Average percent correct scores are plotted for each of the four comparison vowels across consecutive sessions. The criterion for acquisition of the discriminations was that all vowels be discriminated above the 80% correct level for at least 3 days. All discriminations were learned rapidly and typically approached the 90-100% correct level, although rates of learning the discriminations differed among the vowels. Acquisition of the vowel discrimination required 12 and 3 days, respectively, before baboons JE and EE were responding above 80% correct for all comparison vowels. Normative data for the acquisition of these same

vowel discriminations in unexposed baboons ranges from 3 to 15 days. These data thus indicate no differences in the acquisition of these vowel discriminations following single exposures to 12 or 15 Gy.

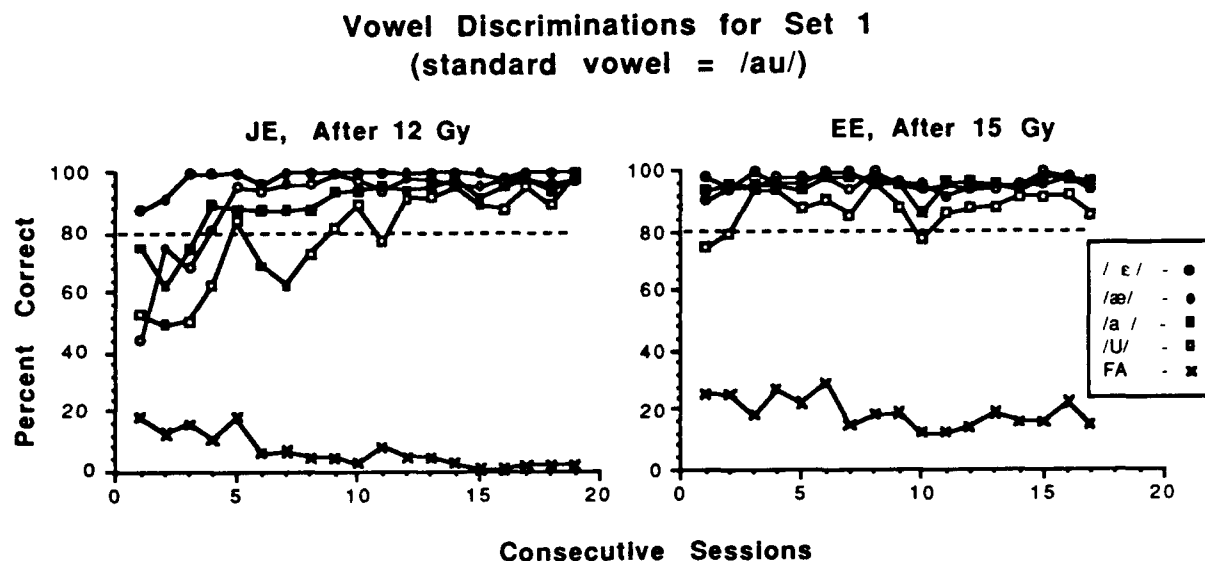


Figure 20. Acquisition of vowel discriminations for vowel set 1 (standard vowel = /au/) following exposure to 12 Gy (baboon JE, left) and 15 Gy (baboon EE, right). Percent correct scores to each vowel is indicated by the designated symbols; open circle /æ/; closed circle /ε/; closed square /a/; open square /u/; "x's" indicate false alarm rates, or responding when no vowel changes occurred.

Figure 21 shows the acquisition of a second set of vowel discriminations for baboons JE and EE following their single exposures to 12 Gy and 15 Gy, respectively. In this set of vowel discriminations, the standard vowel was /æ/. As in Figure 20, average percent correct scores are plotted for each of the four comparison vowels across consecutive sessions. Baboon JE learned these discriminations rapidly. Only the vowel /a/ was difficult to discriminate from the standard vowel initially, and percent correct scores for this vowel were above 80% after the 5th day. Baboon EE appeared to be able to discriminate all vowels at the 80% level after the 4th day; subsequently he had occasional difficulty with the vowel /au/. These data are similar to those for vowel set 1, with the possible exception of baboon EE not consistently approaching the 90-100% level for this second set.

**3.4.5.2 Frequency discrimination analyses.** Pure-tone frequency discrimination performances are relatively difficult to be acquired and maintained in animals (35, 36). Frequency resolving capabilities can be estimated, however, from an animal's ability to discriminate among tokens of steady-state vowels with repeating waveforms. In the present experiments, vowel sounds were recorded at the speaker output and were analyzed via a linear predictive coding (LPC) model of speech stimuli; from the resulting spectra of the vowels, first and second formant

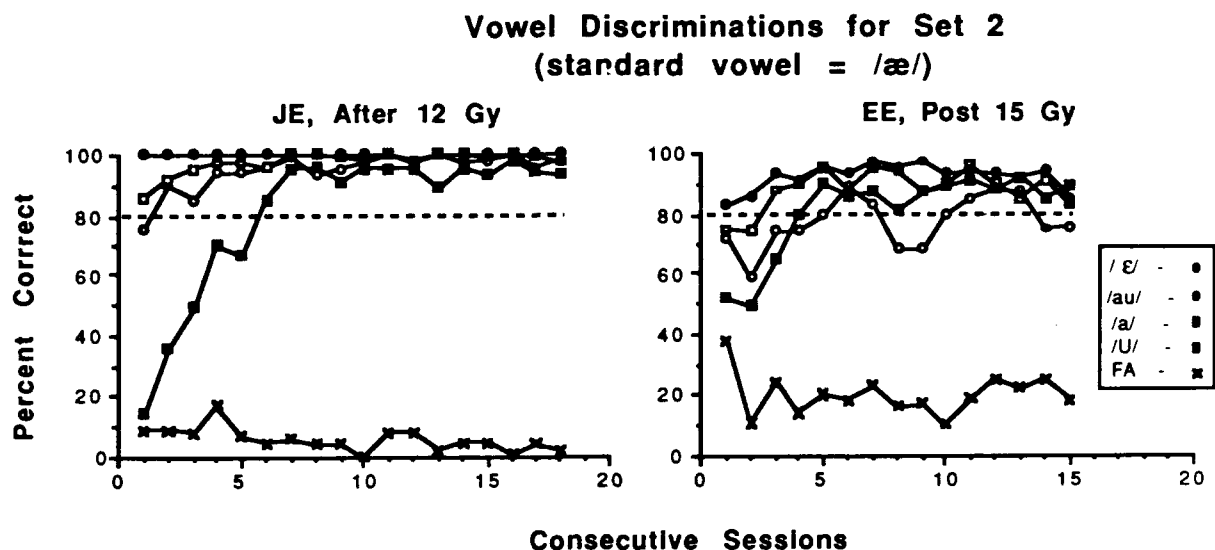


Figure 21. Acquisition of vowel discriminations for vowel set 2 (standard vowel = /æ/) following exposure to 12 Gy (baboon JE, left) and 15 Gy (baboon EE, right). Percent correct scores to each vowel is indicated by the designated symbols; open circle /au/; closed circle /e/; closed square /a/; open square /u/; "x's" indicate false alarm rates, or responding when no vowel changes occurred.

frequencies were extracted, and are given in Table 3. In discriminating the vowel /a/ from the standard vowel (/au/) of the first vowel set, for example, first and second formant differences of 56 and 198 Hz were available for making this discrimination. Thus one can say that, at the very least, baboons can discriminate at least a frequency difference of 198 Hz following a radiation exposure to 12 and 15 Gy. For the second vowel set, the discrimination of the vowel /e/ from the vowel /æ/ rests on first and second formant differences of 50 and 90 Hz, respectively. In this latter case, both baboons could discriminate a formant frequency difference of at least 90 Hz. This value compares to a 10-30 Hz frequency difference limen for pure tones in monkeys (38). In humans, the discrimination of vowel formant changes is about 10 times more difficult than pure-tone frequency discriminations (30). Thus one might expect vowel formant discriminations in monkeys to be considerably higher than pure-tone frequency discriminations. Based on these estimates, then, it appears that there are no obvious effects of these radiation exposure levels on the frequency resolving power of the monkey auditory system.

**Table 3. Formant frequencies and formant differences for all vowels.**

Vowel	Example	F <sub>1</sub> (Hz)	F <sub>2</sub> (Hz)
/au/	caught	593	1039
/ɛ/	let	636	1674
/æ/	cat	726	1724
/a/	lot	649	1237
/U/	book	463	1319

**b. Vowel Set #1 formant differences ( $\Delta F$ ) and Weber fractions ( $\Delta F/F$ ).**

Vowel	$\Delta F_1$ (Hz)	$\Delta F_1/F_1$	$\Delta F_2$ (Hz)	$\Delta F_2/F_2$
/au/ (bkgnd)	----	----	----	----
/ɛ/	43	.073	635	.611
/æ/	133	.224	685	.659
/a/	56	.094	198	.191
/U/	-130	.219	280	.269

**c. Vowel Set #2 formant differences ( $\Delta F$ ) and Weber fractions ( $\Delta F/F$ ).**

Vowel	$\Delta F_1$ (Hz)	$\Delta F_1/F_1$	$\Delta F_2$ (Hz)	$\Delta F_2/F_2$
/æ/ (bkgnd)	----	----	----	----
/ɛ/	-90	.124	-50	.029
/au/	-133	.183	-685	.397
/a/	-77	.106	-487	.282
/U/	-263	.362	-405	.235

## SECTION 4

### CONCLUSIONS

Low-level radiation exposures (1-2 Gy) can produce transient changes in reaction times. When combined with sedation, immediate day-after effects can include slight reductions in baseline reaction times.

Transient increases in reaction times can also occur following low-dose exposures, usually within 1-3 weeks following the exposure. These increases typically recover to normal baseline levels within 2-3 weeks.

Higher radiation exposures (10, 12 and 15 Gy) produced long-term hearing deficits, with the higher exposure dose producing more severe hearing deficits. This hearing loss in general was not frequency-specific.

The severe hearing losses following cumulative dosing at higher exposure levels are most likely to due a sensorineural deficit, since complete loss of function of the tympanic membrane or middle ear ossicles would be expected to produce a hearing loss of no more than 50-60 dB.

These higher radiation doses had less of an effect on visual intensity thresholds. No physical damage to the cornea, iris, lens, or retina was observed.

Exposures of 12 and 15 Gy had no appreciable effect on vowel discrimination abilities.

The frequency resolving power of the auditory system appears to remain intact following single exposures of up to 15 Gy.

## SECTION 5

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## APPENDIX

### DETAILED EXPOSURE HISTORIES FOR BABOONS RECEIVING REPEATED RADIATION EXPOSURES

Subj PA	Dose	Subj SK	Dose	Subj SO	Dose	Subj JE	Dose	Subj EEC	Dose
Day -14	None	Day -36	None	Day -55	None	Day-166	None	Day -57	None
Day -7	None	Day -6	None	Day -35	None	Day-110	None	Day -43	None
Day 0	1.0 Gy	Day 0	1.0 Gy	Day 0	2.5 Gy	Day 0	12.0 Gy	Day 0	15.0 Gy
Day 8	1.0 Gy	Day 21	1.0 Gy	Day 7	2.5 Gy				
Day 28	1.0 Gy	Day 35	1.0 Gy	Day 29	5.0 Gy				
Day 36	1.0 Gy	Day 49	1.0 Gy	Day 112	10.0 Gy				
Day 71	None	Day 63	1.0 Gy						
Day 106	1.0 Gy	Day 77	None						
Day 120	1.0 Gy	Day 93	1.0 Gy						
Day 148	1.0 Gy	Day 105	2.0 Gy						
Day 162	1.0 Gy	Day 224	2.0 Gy						
Day 176	2.0 Gy	Day 238	5.0 Gy						
Day 190	2.0 Gy	Day 252	5.0 Gy						
Day 205	2.0 Gy	Day 315	5.0 Gy						
Day 219	2.0 Gy	Day 336	5.0 Gy						
Day 232	2.0 Gy	Day 434	10.0 Gy						
Day 365	2.0 Gy	Day 490	15.0 Gy						
Day 378	5.0 Gy								
Day 413	5.0 Gy								
Day 427	5.0 Gy								
Day 497	5.0 Gy								
Day 573	10.0 Gy								
Day 643	15.0 Gy								

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